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RESEARCH

Can the free/total psa ratio predict undetected intraductal carcinoma and cribriform pattern at biopsy?

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Abstract

Background Intraductal carcinoma (IDC) and cribriform pattern (Crib) of prostate cancer are recognised as independent prognosticators of poor outcome, both in prostate biopsies and radical prostatectomy (RP) specimens.

Objective This study aimed to determine the predictive value of Free-to-total PSA ratio (FPSAR) in identifying missed IDC/Crib at the time of biopsy as compared to the final surgical specimen.

Materials and methods Patients who underwent RP between January 2015 and December 2022 were included in the study. Predictors of a false negative biopsy were examined using a multivariate logistic regression. Associations between true positive/true negative/false negative biopsies (for IDC/Crib) with FPSAR as primary outcome parameter were determined using Chi-squared test and Kruskal-Wallis test.

Results This study included 639 patients who underwent radical prostatectomy between 2015 and 2022 (Table 1) and had available FPSAR– at the time of biopsy. The median age was 63.0 years (IQR: 58.9–68.0). The median serum PSA before RP was 7.0 ng/ml (IQR: 5.3–9.5). Among the 639 patients, 177 (28%) had Crib, and 97 (15%) had IDC on prostate biopsy, with 54 (9%) patients having both IDC and Crib. Concerning Grade Group distribution at biopsy, there was: GG1 in 62 patients (10%), GG2 in 428 (67%), GG3 in 102 (16%), GG4 in 28 (4%), and GG5 in 19 (3%) patients. On multivariate regression analysis, the following were associated with lower odds of a false-negative IDC/Crib biopsy: Percentage of pattern $4 \geq 10\%$ at biopsy (odds ratio [OR] 0.17, 95% CI 0.10–0.29; $p < 0.001$); higher Gleason score (grade group 4/5) on biopsy (OR 0.38, 95% CI 0.16–0.91; $p = 0.03$) and higher percent of positive cores at biopsy $\geq 33\%$ (OR 0.51, 95% CI 0.29–0.88; $p = 0.02$). FPSAR ≥ 0.10 was not an independent predictor of a false-negative IDC/Crib biopsy ($p > 0.05$).

Conclusions In conclusion, our study's findings suggest that FPSAR is not a reliable biomarker for identifying IDC/Crib status at the time of biopsy. Further research is needed to identify biomarkers or combinations of biomarkers that can improve the diagnostic accuracy for these aggressive variants of PCa.

Patient summary Our study that involved 639 patients shows that FPSAR is not a good marker for detecting aggressive types of PCa, during a biopsy. More research is needed to find better markers or combinations of markers that can help diagnose these aggressive forms of prostate cancer more accurately.

Keywords Prostatic neoplasms · Prostate biopsy · False negatives · Free to total PSA ratio

Introduction

The consensus conference of 2019 by the International Society of Urological Pathology (ISUP) [1] and the white paper from the Genitourinary Pathology Society [2] have established the mandatory inclusion of reporting cribriform growth (Crib) pattern and intraductal prostate cancer (IDC) in routine prostate cancer (PCa) pathology assessments. These growths are identified as biologically aggressive manifestations of PCa, including increased genomic instability and hypoxia [3]. The detection of these patterns in prostatectomy specimens has been consistently linked to increased risks of biochemical recurrence (BCR), metastasis and disease-specific mortality [4–6]. Furthermore,

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recent work from our group revealed that the presence of IDC on biopsy predicts lymphatic metastasis in PSMA PET/CT scans before treatment [7]. Additionally, among patients with BCR and metastatic disease detected via PSMA PET/CT, the presence of Crib is strongly associated with a lymphatic pattern of metastasis [8].

Both IDC and Crib represent adverse features both on radical prostatectomy (RP) specimens and prostate biopsy samples. We have recently found that false-negative biopsy for IDC/Crib (i.e. missed IDC/Crib at biopsy) is independently associated with higher risk of BCR and advanced pathological stage compared to a true negative biopsy [31]. However, there has been a lack of studies investigating how to predict biopsies false-negative for these patterns. A significant challenge associated with this clinical scenario is the notable occurrence of false negatives (exceeding 50% in most series) in identifying IDC/Crib on biopsy when compared to the surgical specimen [9].

Free-to-total PSA ratio (FPSAR) is employed in the ambiguous total PSA range of 4–10 ng/mL, with a higher FPSAR (> 0.25) predicting lower chance of PCa diagnosis and lower Gleason sum [10]. FPSAR has been proposed as a clinical tool for differentiating between PCa and benign prostatic hyperplasia (BPH) in patients with intermediate levels of PSA (4–10 ng/mL) [11, 12]. We hypothesized that a lower FPSAR would be associated with IDC and Crib at final pathology, given the aggressiveness characteristics of these patterns. In this study, we aimed to determine the predictive value of FPSAR in identifying missed IDC/Crib on biopsy pathology.

Materials and methods

Study design, setting, and participants

Patients who underwent RP at Princess Margaret Cancer Center– Toronto, between January 2015 and December 2022 and had an available FPSAR before biopsy were included in the study (Fig. 1). In our institution, FPSAR is calculated by the laboratory when the PSA levels range between 4 ng/ml and 10 ng/ml. Total serum PSA and serum free PSA were quantified by the commercially available *Alinity* method from *Abbott Diagnostics* (Abbott Park, Chicago, IL, USA) according to the manufacturer's instructions [13]. The FPSAR was calculated by dividing the free PSA by the total PSA.

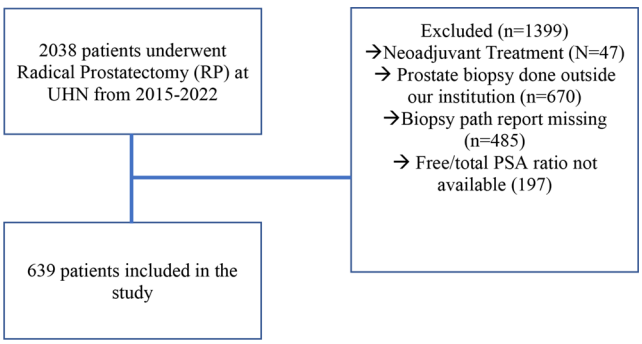

Fig. 1 Flowchart of patient selection

The mandatory reporting of the presence or absence of IDC and Crib in biopsies and radical prostatectomy specimens was adopted at the Department of Pathology in 2015. Subspecialty pathologists read all pathological slides, but not re-reviewed as part of this study. For men who underwent several biopsies before undergoing prostatectomy, the latest biopsy before the surgery was considered. We excluded patients whose biopsy reports did not specifically reference IDC and Crib's presence or absence at biopsy. Although minor differences in methodology may have existed, our institution's regular ultrasound-guided biopsies involve obtaining at least 12 cores from a standard sextant map, and for (multiparametric magnetic resonance imaging) MRI fusion biopsies, a minimum of 3 cores from each target is routinely acquired. All patients were offered a pre-biopsy MRI, following current guidelines [14]. The decision to proceed with an MRI versus upfront biopsy was based on a shared decision-making process with the patient, depending on patient anxiety level, wait time, and whether the post-test result would alter the performance of a biopsy. If the MRI showed a positive lesion (≥ PIRADS 3), patients were typically offered a combined systematic/targeted biopsy approach. Select patients with a prior negative systematic biopsy may have undergone an MRI targeted-only biopsy" A MAGNETOM® Verio 3T 4-channel, phased array surface coil is used in our institution to perform the MRI. The reporting used in the division is PI-RADS v2. The study received Institutional approval (REB: 22-5908). Informed consented for the specific purpose of this study was waived.

Study outcomes

This study aimed to determine the predictive value of FPSAR in identifying missed IDC/Crib at the time of biopsy as compared to the final surgical specimen.

Study variables

IDC was defined as a lumen-spanning proliferation of carcinoma cells distending antecedent ducts or glands. Crib was defined as an expansile area of carcinoma cells without intervening stroma or vasculature and with at least the size of an average size (200 µm diameter) benign gland and with multiple punched-out lumina [15]. Immunostaining for

basal cell markers to help distinguish between IDC and Crib was performed per case decision [16].

Patient age, PSA prior to RP, PI-RADS score, biopsy approach (transrectal ultrasound-guided template or MRI fusion), biopsy and RP Grade Group (GG), percent pattern 4 at biopsy, presence of IDC/Crib at RP and biopsy, pathological stage, percent cores positive, positive margins and lymph node status at RP were reported. Our selection of cut-off values for the FPSAR was grounded in the established precedents set forth by well-documented studies [17].

Statistical analysis

Summary statistics were used to describe continuous and categorial variables. Associations between true positive/true negative/false negative biopsies (for IDC/Crib) with FPSAR were determined using Chi-squared test and Kruskal-Wallis test. Predictors of a false negative biopsy were examined using logistic regression with the following predictors: (1) percentage of pattern 4 disease (< 10% vs. ≥10%); (2) biopsy Gleason grade (GG1 - GG3 vs. GG4-5); (3) PSA before RP; (4) FPSAR (< 0.10 vs. ≥ 0.10; <0.27 vs. ≥ 0.27 and 5) percentage of biopsy positive cores (< 33.3% vs. ≥33.3%);

All statistical analyses were performed using R version 4.2.0 (The R Foundation for Statistical Computing, Vienna, Austria). All hypothesis tests were two-sided and a p-value less than 0.05 was considered statistically significant.

Results

Overall cohort characteristics

This study included 639 patients who underwent radical prostatectomy between 2015 and 2022 (Table 1) and had FPSAR calculated by the laboratory. The median age was 63.0 years (IQR: 58.9–68.0). The median serum PSA before RP was 7.0 ng/ml (IQR: 5.3–9.5). Among the 639 patients, 177 (28%) had Crib, and 97 (15%) had IDC on prostate biopsy, with 54 (9%) patients having both IDC and Crib. Grade Group distribution at biopsy was as follows: GG1 in 62 patients (10%), GG2 in 428 (67%), GG3 in 102 (16%), GG4 in 28 (4%), and GG5 in 19 (3%) patients. Systematic biopsy was performed in 416 (65%) patients, and MRI fusion biopsy (targeted plus systematic) in 223 (35%). Regarding IDC/Crib on RP, the distribution was as follows: 318 (50%) had Crib, 193 (30%) had IDC on final radical prostatectomy pathology, and 151 (24%) patients had both IDC and Crib (Table 1).

Free/Total PSA ratio

Overall cohort

The median FPSAR within the entire cohort was 0.12 (IQR: 0.08–0.16). When we categorized FPSAR values into those < 0.10 and ≥ 0.10, 209 (33%) patients fell into the former category, while 430 (67%) fell into the latter (Supplementary Table 1). Six-hundred and eight patients (95%) had a FPSAR of < 0.27, with 31 (4.9%) with a FPSAR ≥ 0.27.

Association with IDC/Crib Status at prostate biopsy

In terms of IDC/Crib status at biopsy, 163 (26%) patients had a false-negative biopsy, 256 (40%) had a true-negative biopsy, 197 (31%) showed a true-positive biopsy, considering either pattern (Table 2). When comparing false-negative, true-negative and true-positive biopsies for IDC/Crib, we found that the median FPSAR was similar different across the groups (0.11 vs. 0.12 vs. 0.12, respectively; $p = 0.13$). Among the patients with FPSAR < 0.10, 64 (39%), 78 (31%) and 60 (31%) had an IDC/Crib false negative, true negative and true positive biopsy, respectively. Conversely, within the patients with FPSAR ≥ 0.10, 99 (61%), 178 (70%), 137 (70%) had an IDC/Crib false negative, true negative and true positive biopsy, respectively ($p = 0.12$).

When comparing IDC/Crib status at biopsy for FPSAR values < 0.27 and ≥ 0.27, we found that 159 (98%) had a false negative biopsy, 238 (93%) showed a true-negative biopsy and 189 (96%) exhibited a true positive biopsy for FPSAR < 0.27. For FPSAR ≥ 0.27, 4 (3%), 18 (7%) and 8 (4%) disclosed a false negative biopsy, true negative and true positive biopsy respectively ($p = 0.097$).

Association with IDC/Crib status at final RP specimen

Regarding IDC/Crib status at final RP status (Supplementary Table 2), either IDC or Crib was present in 360 (56%) patients and absent in 279 (44%). For FPSAR < 0.10, 85 (31%) did not have IDC or Crib at final pathology, and 124 (34%) did have IDC or Crib. For a FPSAR ≥ 0.10, 194 (70%) did not have IDC or Crib and 236 (66%) had those features ($p = 0.33$). Ninety (6.8%) of the patients with an FPSAR ≥ 0.27 had IDC or Crib at final RP, and 12 (3.3%) did not. Among patients with an FPSAR < 0.27, 260 (93%) had IDC or Crib at the final specimen, and 348 (97%) did not.

Pre-operative predictors of false negative biopsy

On multivariate regression analysis, percentage of pattern 4 ≥ 10% at biopsy (odds ratio [OR] 0.17, 95% CI 0.10–0.29;

Table 1 Overall cohort patient characteristics ($n = 639$)

Variable	
Age in years, median (IQR)	63.0 (58.9–68.0)
Serum pre RP PSA in ng/ml, median (IQR)	7.0 (5.3–9.5)
MRI - PI-RADS, n (%)	
1–3	26 (11.6%)
4–5	197 (88.3%)
Not performed	416
Biopsy Type, n (%)	
Systematic	416 (65.1%)
MRI-fusion	223 (34.9%)
Biopsy Grade Group, n (%)	
Grade Group 1	62 (9.7%)
Grade Group 2	428 (67.0%)
Grade Group 3	102 (16.0%)
Grade Group 4	28 (4.4%)
Grade Group 5	19 (3.0%)
Biopsy intraductal, n (%)	
Present	97 (15.2%)
Absent	542 (84.8%)
Biopsy cribriform, n (%)	
Present	177 (27.7%)
Absent	462 (72.3%)
Biopsy intraductal or cribriform, n (%)	
Both present	54 (8.5%)
Both absent	419 (65.6%)
Intraductal or cribriform present	220 (34.4%)
Percent Cores Positive, %, median (IQR)	44 (31–59)
Percent Pattern 4 at biopsy, %, median (IQR)	10 (5–40)
Radical Prostatectomy Pathological Grade Group, n (%)	
Grade Group 1	70 (11.0%)
Grade Group 2	394 (61.7%)
Grade Group 3	125 (19.6%)
Grade Group 4	19 (3.0%)
Grade Group 5	31 (4.9%)
Pathologic stage on radical prostatectomy specimen, n (%)	
T2	356 (55.9%)
T3a	220 (34.5%)
T3b or worse	61 (9.6%)
Not available	2
Presence of intraductal carcinoma on radical prostatectomy specimen, n (%)	
Yes	193 (30.2%)
No	446 (69.8%)
Presence of cribriform on radical prostatectomy specimen, n (%)	
Yes	318 (49.8%)
No	321 (50.2%)
Presence of intraductal or cribriform on radical prostatectomy specimen, n (%)	
Both present	151 (23.6%)
Both absent	279 (43.7%)
Intraductal or cribriform present	360 (56.3%)
Positive margins, n (%)	
Yes	192 (30.0%)
No	447 (70.0%)
Pelvic lymph node positive, n (%)	
Yes	28 (6.5%)
No	400 (93.5%)
Not performed	211

IQR: Interquartile; PSA: Prostate-specific antigen

Table 2 Free/Total PSA ratio (FPSAR) stratified characteristics stratified by false negative (FN) vs. true positive (TP) vs. true negative (TN) prostate biopsies for IDC/Crib ($n=639$)

Variable	FN ($n=163$)	TP ($n=197$)	TN ($n=256$)	P-value[1]
FPSAR, median IQR	0.110 (0.08–0.15)	0.12 (0.09–0.16)	0.12 (0.09–0.17)	0.13
FPSAR, n (%)				0.12
< 0.10	64 (39.3%)	60 (30.5%)	78 (30.5%)	
≥ 0.10	99 (60.7%)	137 (69.5%)	178 (69.5%)	
FPSAR, n (%)				0.097
< 0.27	159 (97.5%)	189 (95.9%)	238 (93.0%)	
≥ 0.27	4 (2.5%)	8 (4.1%)	18 (7.0%)	

[1]Estimated using Mann-Whitney U tests for continuous variables, and Fisher's Exact or Chi-squared tests for categorical variables

IQR: Interquartile range; PSA: Prostate-specific antigen

Table 3 Univariate and multivariate logistic regression analysis evaluating pre-operative predictors of a false negative biopsy (amongst patients who were positive for IDC/Crib at RP)

Variable	Univariate analysis		Multivariate analysis	
	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
PSA Before RP	0.99 (0.96, 1.03)	0.70		
Percent GG4				
<10%	Reference	**<0.001**	Reference	**<0.001**
>=10%	0.15 (0.09, 0.26)		0.17 (0.10, 0.29)	
Biopsy Grade Group (GG)				
GG1-3	Reference	**0.001**	Reference	**0.030**
GG4-5	0.27 (0.11, 0.57)		0.38 (0.16, 0.91)	
Percent Cores Positive				
<33.3%	Reference	**0.034**	Reference	**0.016**
>=33.3%	0.59 (0.36, 0.96)		0.51 (0.29, 0.88)	
FPSAR				
<0.10	Reference	0.081	Reference	0.13
>=0.10	0.68 (0.44–1.05)		0.69 (0.42, 1.12)	
<0.27	Reference	0.40		
>=0.27	0.59 (0.16–1.92)			

$p<0.001$), higher Gleason score (grade group 4/5) on biopsy (OR 0.38, 95% CI 0.16–0.91; $p=0.03$) and higher percent of positive cores at biopsy ≥ 33% (OR 0.51, 95% CI 0.29–0.88; $p=0.016$) were associated with lower odds of a false negative IDC/Crib biopsy. On the other side, FPSAR ≥ 0.10 was not an independent predictor of a false negative IDC/Crib biopsy (Table 3).

Discussion

Prostate biopsies are not accurate on detecting IDC/Crib with the sensitivity of detection at around 50% [9]. MRI has also been associated with controversial results in predicting IDC/Crib [18]. Pinto et al. demonstrated that the extent of disease for Crib-containing tumors is difficult to capture on MRI. Additionally, when comparing MRI lesions of similar dimensions and PIRADS scores, Crib tumors appear to have larger cancer yield on biopsy [19]. Mikoshi et al. also reported that neither the presence nor the percentage of IDC was related to MRI detectability [20].

Masoomian et al. conducted a study analyzing the concordance rates of Crib architecture in 245 paired biopsies and surgical specimens. Conversely, it was observed that among GG2 biopsy patients, both false-negative and true-positive biopsies exhibited a more advanced stage compared to true-negative biopsies upon radical prostatectomy [21]. In addition, Hollemans et al. [22] showed that men with true-positive biopsies had a significantly shorter post-operative BCR-free survival compared to those with false-negative biopsies. For all these reasons there is a (still unmet) need for biomarkers that can differentiate false negative from true negative biopsies for those features. In our study, we sought to assess whether the FPSAR could serve as a reliable biomarker for predicting missed IDC and Crib at Biopsy.

Contrary to our initial hypothesis, FPSAR did not show significant predictive value for the detection of IDC/Crib at biopsy. The median FPSAR across false-negative, true negative, and true positive biopsy groups was similar (0.11 vs. 0.12 vs. 0.12, respectively, $p=0.13$). Additionally, in multivariate analysis, FPSAR ≥ 0.10 was not associated with a reduced likelihood of a false negative biopsy for IDC/Crib

($p > 0.05$). This suggests that FPSAR is not a distinguishing factor for IDC/Crib status at biopsy.

However, other traditional histopathological factors were found to be independent predictors of a lower risk of false-negative biopsies for IDC/Crib. A higher percentage of pattern 4 disease (≥ 10%) at biopsy (OR 0.17, 95% CI 0.10–0.29, $p < 0.001$) was an independent predictor of detecting IDC/Crib, as was a higher biopsy Gleason grade (GG 4/5) (OR 0.38, 95% CI 0.16–0.91, $p = 0.03$), supporting the well-established role of higher Gleason scores as indicators of more aggressive disease. Furthermore, a higher percentage of positive biopsy cores (≥ 33%) (OR 0.51, 95% CI 0.29–0.88, $p = 0.02$) also increased the likelihood of detecting IDC/Crib, reinforcing the notion that more extensive biopsy involvement is associated with improved detection of these aggressive cancer features [9].

Although FPSAR was not a biomarker for false-negative biopsies for IDC/Crib in this clinical context, it has demonstrated clinical utility not only in differentiating PCa from benign prostatic hyperplasia. PSA is found in peripheral blood in two primary forms: a catalytically active form that is complexed with protease inhibitors, predominantly alpha-1-antichymotrypsin, and a catalytically inactive form that circulates freely as free PSA (fPSA) [23]. In individuals without PCa, approximately 70–90% of total PSA (tPSA) is bound in complexes, while 10–30% is present as fPSA [24]. In the case of PCa cells, PSA is less subject to proteolytic processing and undergoes fewer internal cleavages [23]. This leads to a larger proportion of PSA circulating in its complexed form, hence a lower FPSAR. Clinical studies have corroborated this distinction, revealing that men with a lower FPSAR, have a higher probability of harboring prostate cancer compared to patients with similar risk profiles but higher FPSAR [24, 25]. Therefore, FPSAR is frequently utilized to enhance the specificity of PSA screening, particularly for men with a tPSA in the range of 4 to 10 ng/mL [26, 27].

Furthermore, the absence of a significant association between FPSAR and IDC/Crib detection in our study contrasts with its demonstrated clinical utility in predicting adverse pathological outcomes at radical prostatectomy. A lower FPSA was significantly associated with capsular penetration, positive margins, a higher Gleason score, greater percentage of cancer, and greater cancer volume [28]. There is also data indicating that low-grade and high-grade prostate cancers have quite similar total PSA values; however, they differ in their FPSA levels, with the latter being lower in the high-grade group [22]. Although several studies have shown that FPSA ratios decrease significantly with increasing Gleason scores [24, 25], to the best of our knowledge, the association between FPSAR and the presence of IDC/Crib has not yet been reported. Previous studies have demonstrated that higher PSA levels are associated with the presence of Crib morphology in final pathology [22, 23]; however, FPSAR was not included in these analyses. This may reflect the unique biological features of IDC/Crib [29], which ultimately do not contribute to PSA proteolytic processing dynamics and are not captured by FPSAR.

This study's limitations stem from its single-center design and the retrospective nature of the research, which may introduce selection bias. Nonetheless, the robustness of the study is underpinned by the prospective collection of data from a recent patient cohort. This was enhanced by the systematic reporting of IDC/Crib by a dedicated urogenital pathologist in an academic institution with a specialized focus on IDC/Crib, helping to alleviate some of the biases typically encountered in retrospective pathology analyses. A notable shortfall, however, is the absence of details on IDC/Crib volume in the radical prostatectomy pathology reports, which limits our ability to fully discern the relationship between the volume of IDC/Crib, FPSAR, and the incidence of false-negative findings.

Our group recently found that TMBIM1 [30], also known as Bax inhibitor 1 (BI-1), is associated with IDC/Crib at biopsy. Bax inhibitor 1 (BI-1) plays a crucial role in regulating apoptosis and calcium homeostasis by inhibiting the activity of the pro-apoptotic protein Bax and protecting cells from apoptosis induced by various stimuli. This underscores the need for further research to validate this finding and to elucidate new biomarkers for detecting these aggressive features.

Conclusions

In conclusion, our study's findings indicate that the FPSAR does not serve as a discriminating biomarker for identifying IDC/Crib status at the point of biopsy. Further research is necessary to elucidate biomarkers or combinations thereof that can enhance the diagnostic precision for these aggressive prostate cancer variants.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00345-024-05369-4.

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Data availability The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request. Data are located in controlled access data storage at Princess Margaret Cancer Centre.

Declarations

Ethical approval Appropriate ethics approval was obtained from the University Health Network research ethics board.

Previous presentations None.

Competing interests The authors declare no competing interests.

References

1. van Leenders GJLH, van der Kwast TH, Iczkowski KA (2021) The 2019 International Society of Urological Pathology Consensus Conference on prostate Cancer grading. Eur Urol 79(6):707–709
2. Epstein JI, Amin MB, Fine SW, Algaba F, Aron M, Baydar DE et al (2021) The 2019 Genitourinary Pathology Society (GUPS) White Paper on contemporary grading of prostate Cancer. Arch Pathol Lab Med 145(4):461–493
3. Chua MLK, Lo W, Pintilie M, Murgic J, Lalonde E, Bhandari V et al (2017) A prostate Cancer Nimbosus: genomic instability and SChLAP1 dysregulation underpin aggression of Intraductal and Cribriform Subpathologies[Figure presented]. Eur Urol 72(5):665–674
4. Bernardino RM, Carvalho R, Severo L, Alves M, Papoila AL, Pinheiro C (2020) Prostate cancer with cribriform pattern: exclusion criterion for active surveillance? Arch Ital Urol Androl 92(3):235–238
5. Kweldam CF, Wildhagen MF, Steyerberg EW, Van Der Bangma CH, Van Leenders GJLH (2015) Cribriform growth is highly predictive for postoperative metastasis and disease-specific death in Gleason score 7 prostate cancer. Mod Pathol 28(3):457–464
6. Hollemans E, Verhoef EI, Bangma CH, Rietbergen J, Helleman J, Roobol MJ et al (2019) Large cribriform growth pattern identifies ISUP grade 2 prostate cancer at high risk for recurrence and metastasis. Mod Pathol 32(1):139–146
7. Bernardino R, Sayyid RK, Lajkosz K, Al-Daqqaq Z, Tiwari R, Cockburn J et al Intraductal Prostate Cancer Affinity for Lymphatic-Predominant Metastases Through 18F-DCFPyL–Prostate-Specific Membrane Antigen–Positron Emission Tomography/CT Scans in Pretreatment Prostate Cancer Patients. J Urol [Internet]. 2024 Feb [cited 2024 Feb 6]; https://pubmed.ncbi.nlm.nih.gov/38299501/
8. Bernardino R, Sayyid RK, Al-Daqqaq Z, Tiwari R, Cockburn J, Vijayakanthan S et al Lymphotropic Pattern of Prostate-specific Membrane Antigen–detected Metastases Among Biochemically Recurrent Radical Prostatectomy Patients with Cribriform Disease. Eur Urol Focus [Internet]. 2023 May [cited 2023 Jun 1];0(0). http://www.eu-focus.europeanurology.com/article/S2405456923001165/fulltext
9. Bernardino RM, Sayyid RK, Lajkosz K, Al-Daqqaq Z, Cockburn JG, Chavarriaga J et al Limitations of Prostate Biopsy in Detection of Cribriform and Intraductal Prostate Cancer. Eur Urol Focus [Internet]. 2023 Sep [cited 2023 Sep 24]; https://pubmed.ncbi.nlm.nih.gov/37696743/
10. Magklara A, Scorilas A, Catalona WJ, Diamandis EP The Combination of Human Glandular Kallikrein and Free Prostate-specific Antigen (PSA) Enhances Discrimination Between Prostate Cancer and Benign Prostatic Hyperplasia in Patients with Moderately Increased Total PSA. Clin Chem [Internet]. 1999 Nov 1 [cited 2024 Feb 4];45(11):1960–6. https://doi.org/10.1093/clinchem/45.11.1960
11. Luderer AA, Chen YT, Soriano TF, Kramp WJ, Carlson G, Cuny C et al (1995) Measurement of the proportion of free to total prostate-specific antigen improves diagnostic performance of prostate-specific antigen in the diagnostic gray zone of total prostate-specific antigen. Urology [Internet]. [cited 2024 Jan 14];46(2):187–94. https://pubmed.ncbi.nlm.nih.gov/7542820/
12. Magklara A, Scorilas A, Catalona WJ, Diamandis EP (1999) The Combination of Human Glandular Kallikrein and Free Prostate-specific Antigen (PSA) Enhances Discrimination Between Prostate Cancer and Benign Prostatic Hyperplasia in Patients with Moderately Increased Total PSA. [cited 2024 Jan 14]; https://academic.oup.com/clinchem/article/45/11/1960/5643412
13. Ferraro S, Biganzoli G, Bussetti M, Castaldi S, Biganzoli EM, Plebani M Managing the impact of inter-method bias of prostate specific antigen assays on biopsy referral: the key to move towards precision health in prostate cancer management. Clin Chem Lab Med [Internet]. 2022 Jan 1 [cited 2024 May 14];61(1):142–53. https://pubmed.ncbi.nlm.nih.gov/36322977/
14. Prostate Cancer - INTRODUCTION - Uroweb [Internet]. [cited 2023 May 29]. https://uroweb.org/guidelines/prostate-cancer
15. Treurniet KM, Trudel D, Sykes J, Evans AJ, Van Der Finelli A (2014) Downgrading of biopsy based Gleason score in prostatectomy specimens. J Clin Pathol [Internet]. [cited 2023 Sep 26];67(4):313–8. https://pubmed.ncbi.nlm.nih.gov/24403214/
16. Masoomian M, Downes MR, Sweet J, Cheung C, Evans AJ, Fleshner N et al (2019) Concordance of biopsy and prostatectomy diagnosis of intraductal and cribriform carcinoma in a prospectively collected data set. Histopathology 74(3):474–482
17. Hoffman RM, Clanon DL, Littenberg B, Frank JJ, Peirce JC (2000) Using the Free-to-total Prostate-specific Antigen Ratio to Detect Prostate Cancer in Men with Nonspecific Elevations of Prostate-specific Antigen Levels. J Gen Intern Med [Internet]. [cited 2024 Apr 15];15(10):739. http://www.pmc/articles/PMC1495603/
18. Bernardino R, Fleshner N, Re Sensitivity of Multiparametric MRI and Targeted Biopsy for Detection of Adverse Pathologies (Cribriform Gleason Pattern 4 and Intraductal Carcinoma): Correlation of Detected and Missed Prostate Cancer Foci with Whole Mount Histopathology. Eur Urol [Internet]. 2023 [cited 2023 May 12]; https://pubmed.ncbi.nlm.nih.gov/36792385/
19. Belue MJ, Blake Z, Yilmaz EC, Lin Y, Harmon SA, Nemirovsky DR et al Is prostatic adenocarcinoma with cribriform architecture more difficult to detect on prostate MRI? Prostate [Internet]. 2023 Dec 1 [cited 2024 Jan 4];83(16):1519–28. https://pubmed.ncbi.nlm.nih.gov/37622756/
20. Mikoshi A, Miyai K, Hamabe F, Edo H, Ito K, Matsukuma S et al (2022) MRI-detectability and histological factors of prostate cancer including intraductal carcinoma and cribriform pattern. Prostate 82(4):452–463
21. Masoomian M, Downes MR, Sweet J, Cheung C, Evans AJ, Fleshner N et al Concordance of biopsy and prostatectomy diagnosis of intraductal and cribriform carcinoma in a prospectively collected data set. Histopathology [Internet]. 2019 Feb 1 [cited 2023 May 28];74(3):474–82. https://pubmed.ncbi.nlm.nih.gov/30160779/
22. Hollemans E, Verhoef EI, Bangma CH, Schoots I, Rietbergen J, Helleman J et al Concordance of cribriform architecture in matched prostate cancer biopsy and radical prostatectomy

specimens. Histopathology [Internet]. 2019 [cited 2023 May 28];75(3):338–45. https://pubmed.ncbi.nlm.nih.gov/31045262/
23. Balk SP, Ko YJ, Bubley GJ Biology of prostate-specific antigen. J Clin Oncol [Internet]. 2003 Jan 15 [cited 2024 Apr 13];21(2):383–91. https://pubmed.ncbi.nlm.nih.gov/12525533/
24. Murray NP, Reyes E, Orellana N, Fuentealba C, Dueñas R (2014) A comparative performance analysis of total PSA, percentage free PSA, PSA velocity, and PSA density versus the detection of primary circulating prostate cells in predicting initial prostate biopsy findings in Chilean men. Biomed Res Int [Internet]. [cited 2024 Apr 13];2014. https://pubmed.ncbi.nlm.nih.gov/25101294/
25. Elabbady AA, Khedr MM Free/total PSA ratio can help in the prediction of high gleason score prostate cancer in men with total serum prostate specific antigen (PSA) of 3–10 ng/ml
26. Lattouf JB Reflexive ordering of percent free PSA in patients: Do we need to ask the question? Canadian Urological Association Journal [Internet]. 2010 Oct [cited 2024 Apr 13];4(5):321. http://www.pmc/articles/PMC2950780/
27. Magklara A, Scorilas A, Catalona WJ, Diamandis EP The Combination of Human Glandular Kallikrein and Free Prostate-specific Antigen (PSA) Enhances Discrimination Between Prostate Cancer and Benign Prostatic Hyperplasia in Patients with Moderately Increased Total PSA. Clin Chem [Internet]. 1999 Nov 1 [cited 2024 Apr 13];45(11):1960–6. https://doi.org/10.1093/clinchem/45.11.1960
28. Catalona WJ (1996) Clinical utility of measurements of free and total prostate-specific antigen (PSA): A review. In: Prostate. pp. 64–9
29. Wong HY, Sheng Q, Hesterberg AB, Croessmann S, Rios BL, Giri K et al Single cell analysis of cribriform prostate cancer reveals cell intrinsic and tumor microenvironmental pathways of aggressive disease. Nature Communications 2022 13:1 [Internet]. 2022 Oct 13 [cited 2024 Sep 22];13(1):1–21. https://www.nature.com/articles/s41467-022-33780-1
30. Bernardino R, Carvalho AS, Hall MJ, Alves L, Leão R, Sayyid R, et al. Profiling of urinary extracelullar vesicle protein signatures from patients with cribriform and intraductal prostate cancer in a cross-sectional study. Sci Rep. 2024. PMID: 3944354439443544.
31. Bernardino RM, Yin LB, Cockburn JG, Wettstein M, Sayyid RK, et al. Undetected Cribriform and Intraductal Prostate Cancer at biopsy is associated with adverse outcomes. Prostate Cancer Prostatic Dis. 2024. PMID: 39433886.

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